
# The Regulatory Capture of the FDA

## Description

USA: This week, three members of an 11 member FDA advisory committee of experts resigned in protest over the FDA's approval of Aduhelm (aducanumab) for the treatment of Alzheimer's disease. These resignations are extremely unusual, but in this case, understandable.

Aduhelm was approved by the agency despite the fact that both pivotal trials were stopped early because they were judged to be futile, the FDA's own statistical reviewer did not support approval, and the FDA advisory committee reviewing the application voted it down overwhelmingly. Additionally, in a survey conducted by Endpoint News, whose readership is heavily weighted to biopharmaceutical industry staffers and executives, over 80 percent consider the approval to be a bad idea. So, how did Aduhelm's June 7 approval happen? Two words: regulatory capture.

Regulatory capture is defined as when a supposedly objective regulatory agency ends up promoting the ends of the industries they are regulating. The FDA has been captured for quite a while. In a 2016 study published in the British Medical Journal, the majority of the FDA's hematology-oncology reviewers who left the agency ended up working or consulting for the biopharmaceutical industry. In another investigation by *Science* magazine, 11 of 16 FDA reviewers who worked on 28 drug approvals and subsequently left the agency are working or consulting for the companies they recently regulated.

For example, Dr. Thomas Laughren, a former director of psychiatric products for the FDA, who had a history of less than objective actions while at the agency, left the FDA in 2012 and started a consultancy to help companies focused on psychiatric products navigate the regulator's approval process. One of these companies is AstraZeneca, maker of Seroquel. He was instrumental in getting Seroquel a broader approval in 2009, going so far as to personally minimize questions about cardiac risk related to the drug at an FDA advisory committee meeting. After approval, however, there was no hiding from these side effects and a warning label had to be added to the drug in 2011.

Back in 2016, there was a major controversy related to the actions of Dr. Janet Woodcock, the current acting FDA commissioner, while she was the director of the Center for Drug Evaluation and Research (CDER). The FDA, at the behest of Woodcock, overruled significant internal dissension to approve Exondys, a therapy for Duchenne muscular dystrophy (DMD), a rare and severe disease which

currently has an annual treatment cost of around $1 million per patient per year. Luckily for the public, the FDA published the internal dissension with their approval documents.

One of the most vocal objections came from Dr. Ellis Unger, who was director of the Office of Drug Evaluation at CDER. According to Unger, Woodcock was intensely involved in the review of Exondys from the very beginning and decided to approve the drug before the actual review team had finished its own recommendation. And besides interference, Unger was very vocal in his belief that Exondys is ineffective, even calling it a “scientifically elegant placebo.” Exondys was approved based on its impact on dystrophin which is thought to be a biomarker for efficacy. Unger pointed out that the impact on dystrophin is so small that if you had 10 inches of snow on the sidewalk, the drug effect would be equal to 1/32 of an inch. Additionally, Dr. John Jenkins, who was the director of new drugs at the agency, also voiced opposition to the approval and retired soon afterwards.

Why did Woodcock fight so fiercely for the approval of Exondys? The worst reason was probably due to worries over the stock price of Sarepta, the manufacturer of Exondys. In her presentation in front of the Agency Scientific Dispute Process Review Board (SDR Board), Woodcock noted that Sarepta “needed to be capitalized” and mentioned how the stock reacted to different FDA actions. She also suggested that if Sarepta did not receive approval, the company might have insufficient capital to continue its study of Exondys and other drugs in the company’s pipeline. Or in essence, we have to approve this drug so they can study it.

And we shouldn’t forget the political pressure, of course. Within the approval documents it was noted that both Unger and Woodcock received significant correspondence from Congress and the public, urging approval for the drug. It was also probably not a coincidence that Sarepta significantly increased its lobbying spending ahead of and during the approval process. Lobbying continues to have a fantastic return on investment, as Exondys revenues are currently over $400 million per year (after spending less than a year’s worth of revenues from one patient on the activity on an annual basis).

Now let’s get back to Aduhelm. In March of 2019, Biogen’s two identically designed randomized controlled studies looking at Aduhelm in mild Alzheimer’s patients (trials 301 and 302) were stopped due to the data safety monitoring board judging them to be futile and unlikely to produce a clinically meaningful benefit. Then in October of that year, Biogen announced that after receiving additional data from one of the trials, they decided to file for approval of the high dose tested (10mg/kg) with the FDA. This despite the fact that the benefit was only seen in trial 302, while in trial 301 patients on the high dose actually did worse than patients on placebo. Even the pooled data, combining that from both trials, did not show a significant benefit for the high dose.

After Biogen made the decision to move forward, the company then went to work on the narrative. At the Clinical Trials on Alzheimer's Disease conference in December 2019, during a session to discuss the data, no skeptics or even statisticians were given a platform to speak. Additionally, no open question-and-answer segment was allowed and all microphones were removed from around the room. This was highly unusual, especially given that question-and-answer sessions are the rule at a medical conference. Even more shocking was that Biogen and the FDA released joint briefing documents for the meeting of the FDA Advisory Committee (a panel of experts convened prior to a drug's approval) to discuss the safety and efficacy of the drug. In my 22 years looking at the biotechnology sector, I don't remember this ever happening. Typically, the FDA has one set of briefing documents where they discuss the data from their point of view, and the company has a different set.

Despite this questionable degree of collaboration, if not collusion, the meeting did not go well for Biogen. Statisticians typically do not like the acrobatics required to make a negative study into a positive one, and the FDA's statistician at the meeting, Dr. Tristan Massie, was no different. He concluded that the evidence was conflicting and that approval might actually negatively impact the development of more effective treatments, both with regard to the design of future trials as well as recruitment (patients often would prefer to use an approved drug over one in clinical trials). The advisory committee shared his view and on the key question regarding whether trial 302 provided evidence of effectiveness of the drug; not a single committee member voted yes and 10 voted no, with one abstention. A pretty overwhelmingly negative response.

And yet, the FDA approved it anyway. Even worse, the actual drug label, which is what physicians and patients review when considering a drug, reads like it was written by Biogen's marketing team. First, the label indicates that it is approved for the treatment of all stages of Alzheimer's disease, even though it was only tested in mild patients and had meager efficacy even there. This greatly inflates the addressable market size, as now all six million Americans with Alzheimer's are eligible for therapy. Given the company decided to price the drug well ahead of any projections, at $56,000 per patient per year (the Institute for Clinical and Economic Review calculated a fair price to be between $2,500 and $8,300), this drug could be a real budget buster. And this six million patient estimate only includes people over the age of 65, hence they will be covered by Medicare (specifically Medicare Part B as it is an infusion). In 2019, total spending by Medicare Part B was $37 billion. If just 15 percent of patients with Alzheimer's decide to go on Aduhelm, that would equal $50 billion in spending.

The FDA also stated that they approved Aduhelm because of reduction in amyloid plaques—misfolded proteins between nerve cells—even though that was not the primary endpoint of either study and there is actually no evidence that a reduction in plaques improves anything. Even in the case of Aduhelm, both studies indicated a significant reduction in plaques and yet one of the studies showed a placebo outperforming the high dose. We've seen a similar scenario play out before. Merck's Verubecestat was able to show 60 to 80 percent reductions in plaques and was still unable to show any clinical benefit (and was even worse than placebo on several important measures).

There were a couple of additional irregularities in the label which seem to benefit Biogen. Trial 301 was the "bad" one while trial 302 was the "good" one. The label reverses the numbering so that the "good" trial is referred to as "Study 1," which allows them to speak about that data first and in detail. When discussing "Study 2," the label excludes any presentation of the clinical data that showed that placebo patients did better than patients who received the approved dose, despite the fact that this occurred

with regard to the primary endpoint of the trial. That's a very key piece of information that would be important for patients and physicians to know about when considering therapy and whether the benefit outweighs the risk of side effects, which include cerebral microhemorrhage (19 percent of patients who received the high dose) and cerebral edema (35 percent of patients).

Why did the FDA do all of this? Besides the usual incentives for post-FDA careers, there were likely political considerations at work, as in the case of Sarepta (and remember Janet Woodcock, who heavily influenced that decision, is currently acting FDA commissioner). Less than two weeks prior to the approval, President Joe Biden said that "if we don't do something about Alzheimer's in America… every single [hospital bed] will be occupied in the next 15 years with an Alzheimer's patient." Guess which 2020 candidate was the largest recipient of campaign funds by a large margin from Biogen and affiliated parties? Joe Biden, with $76,241. And like Sarepta, Biogen also significantly increased their lobbying ahead of the FDA decision, with 2020 being a record year and 2021 being a record first quarter. The FDA did not publish the internal deliberations like they did with Sarepta, but my guess is that they wouldn't necessarily be that different and would indicate similar pressures.

I have a lot of respect for the FDA and I think the vast majority of reviewers are looking to do the right thing, but the system is broken and there need to be more firewalls to insulate the FDA from manipulation. A 2006 survey of FDA scientists indicated that 18.4 percent of them had "been asked, for non-scientific reasons, to inappropriately exclude or alter technical information or their conclusions in a FDA scientific document." I have to imagine a similar survey wouldn't show any better results today.

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